Available online at www.sciencedirect.com

SCIENCE DIRECT®

Journal of Molecular Catalysis A: Chemical 202 (2003) 163–170

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

www.elsevier.com/locate/molcata

Heterogeneous asymmetric reactions Part 32. High enantioselectivities in the hydrogenation of activated ketones on cinchona alkaloid modified platinum-alumina catalysts☆

Károly Felföldi[b], Katalin Balázsik[a], Mihály Bartók[a,*]

[a] *Organic Catalysis Research Group of the Hungarian Academy of Sciences, Dóm tér 8, H-6720 Szeged, Hungary*
[b] *Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720 Szeged, Hungary*

Received 15 October 2002; accepted 24 February 2003

Abstract

The modifier concentration dependence of rate and enantioselectivity (ee) was investigated of the diethyl-2-oxoglutarate (EOG) and pyruvaldehyde dimethyl acetal (PADA) hydrogenations catalyzed by cinchona alkaloid modified Pt-alumina catalysts. Using the E 4759 catalyst in acetic acid under mild experimental conditions (room temperature, hydrogen pressure 1 bar) an optical yield of 95–97% can be achieved. Recent studies on activated ketones of different structures (EtPy: ethyl pyruvate, EOG, EBF: ethyl benzoylformate, PADA) carried out under identical experimental conditions have called attention to the role of additional factors to be considered for the interpretation of the mechanism of Orito's reaction.

Keywords: Enantioselective; Hydrogenation; Platinum-alumina; Pyruvaldehyde dimethyl acetal; Diethyl 2-oxoglutarate; Cinchona alkaloid

1. Introduction

The preparation of chiral pharmaceuticals and agrochemicals by direct asymmetric synthesis is one of the most fascinating areas in contemporary chemical research [1,2]. Owing to the recent environmental considerations and safety concerns, the use of heterogeneous asymmetric methods [3–5] such as enantioselective hydrogenation [6–11] are especially preferable.

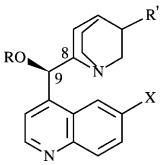
The cinchona alkaloid (Scheme 1) modified platinum catalyst system developed by Orito et al. [12] is a successful example in this field with wide interest. The method was found to be of excellent performance in the hydrogenation of activated ketones [13–22]. This unique catalytic system is still in the focus of interest. Recently, mainly two major routes are followed, first new application possibilities opened up widening the classes of substrates. On the other hand, extensive efforts were carried out to get more insight into of the mechanism.

Results in the field of the enantioselective hydrogenation of activated ketones are summarized in Table 1. From these, the preparation of two new chiral synthons, lactaldehyde dimethyl acetal (LADA) and

☆ Part 31. M. Bartók, M. Sutyinszki, K. Felföldi, Gy. Szöllősi, Chem. Commun. (2002) 1130.

* Corresponding author. Fax: +36-62-544-200.
E-mail address: bartok@chem.u-szeged.hu (M. Bartók).

1381-1169/03/$ – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S1381-1169(03)00194-8

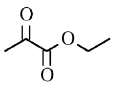
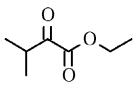
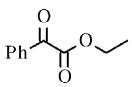
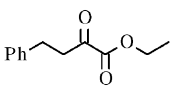
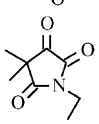
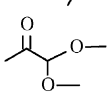
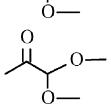
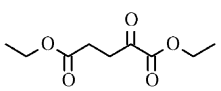


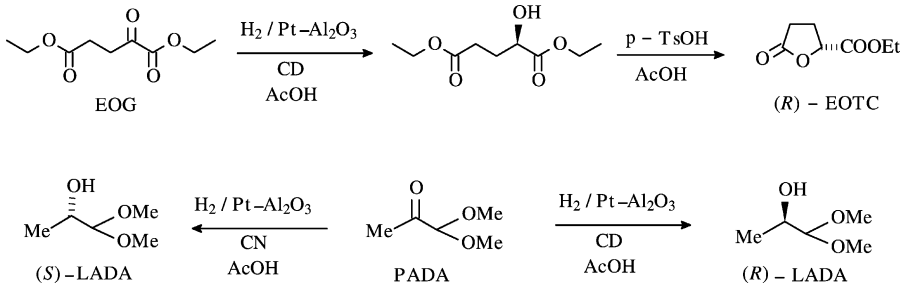
Modifier	X	R	R'
cinchonidine (CD), C8=*S*, C9=*R*	H	H	$CH=CH_2$
dihydrocinchonidine (DHCD), C8=*S*, C9=*R*	H	H	Et
9(*R*)-methoxy-10,11-dihydrocinchonidine (MeOHCD), C8=*S*	H	Me	Et
cinchonine (CN), C8=*R*, C9=*S*	H	H	$CH=CH_2$
quinine (QN), C8=*S*, C9=*R*	MeO	H	$CH=CH_2$
quinidine (QD), C8=*R*, C9=*S*	MeO	H	$CH=CH_2$

Scheme 1.

ethyl-5-oxotetrahydrofuran-2-carboxylate (EOTC) is described in this paper. The synthesis of both of these chiral synthons has only been reported in preliminary communications [18,19,21]. The extensive experience accumulated in the course of our wide-ranging studies on ethyl pyruvate (EtPy) and ethyl benzoylformate (EBF) has naturally been deployed for the optimization of experimental conditions [14,23,24]. The enantioselective hydrogenation of pyruvaldehyde dimethyl acetal (PADA), diethyl-2-oxoglutarate (EOG) and the

Table 1
High enantioselectivities in the hydrogenation of activated ketones over cinchona modified Pt/alumina (AcOH: acetic acid, T: toluene)

Reactant	Modifier	Solvent	H_2 pressure (bar)	Temperature (K)	ee (*R*) (%)	Reference
	CD	AcOH	10	298	97	[13]
	DHCD	AcOH/T	25	273	95	[22]
	DHCD	AcOH/T	25	273	98	[14]
	DHCD	AcOH	5.8	290	91	[15]
	CD	T	70	265	91	[16]
	CD	T	70	288	91	[17]
	CD	AcOH	1	293	93	[18]
	MeOHCD	AcOH	60	298	97	[19]
	CD	T/TFA	10	273	91	[20]
	MeOHCD	AcOH	1	293	93	[21]



Scheme 2.

subsequent cyclization of EOG to EOTC are shown in Scheme 2.

The present publication has a dual aim: on the one hand, to present experimental evidence for the preparation of two new chiral synthons [(*R*)-LADA and (*R*)-EOTC] in outstandingly high enantioselectivity (ee); on the other hand, to adequately compare these experimental results with data obtained under identical experimental conditions with other substrates. These studies may highlight additional factors to be taken into account in the interpretation of the mechanism of the Orito reaction.

2. Experimental

2.1. Materials

CD, CN, QN, QD, EtPy, PADA, 2-ketoglutaric acid and AcOH were purchased from Fluka. EtPy and PADA were distilled before use to attain 99.5% purity. The EOG was prepared on the basis of a literature procedure [25]. DHCD was prepared by hydrogenation of CD (Pd/C, 1N H_2SO_4/H_2O, 1 bar, 298 K) and used after crystallization. MeOHCD was kindly donated by Dr. Martin Studer (Novartis, Basel, Switzerland).

In this study two well known Pt/Al_2O_3 reference catalysts (Engelhard 4759, denoted E4759 and Johnson Matthey 94, denoted JMC94) were used. The properties of most often used E4759 are the following [26]: Pt-content 5% (w/w); Pt dispersion: as received 38%, after pretreatment 27%; mean Pt particle size 4.5 nm; support γ-Al_2O_3; specific surface area 168 $m^2\,g^{-1}$; mean pore radius 2 nm; specific pore volume 0.27 ml g^{-1}. E4759 was pretreated before use in a fixed bed reactor by flushing with 30 ml min^{-1} helium at 300–673 K for 30 min and 30 ml min^{-1} hydrogen at 673 K for 100 min. After cooling to room temperature in hydrogen, the catalyst was flushed with helium for 30 min and was stored under air before use.

2.2. Hydrogenation

Hydrogenation was performed in an atmospheric batch reactor or in a Berghof Bar 45 autoclave at room temperature. The catalytic system including catalyst and AcOH was purged three times with hydrogen and after prehydrogenation (30 min), the calculated amount of modifier and 1 mmol reactant were introduced and stirred (1200 rpm) in the presence of hydrogen for the required reaction time (usually 10–60 min). The standard conditions were: 25 mg E4759, 2 ml AcOH, 1 bar H_2, 296–298 K, 1200 rpm, 0.12 ml PADA, 0.2 ml EOG. The quantification of conversion and ee are based on GC data. After hydrogenation of EOG, the hydroxyester obtained was subjected to a cyclization reaction with *p*-toluenesulfonic acid according to the literature procedure [25]. During the reaction no racemization or inversion occurred as a result the ee of the cyclic products corresponded to that of the open chain hydroxy esters. Product identification was carried out by GC–MS (HP5890 GC-HP5970 MSD) and ^{1}H NMR spectrometry (Bruker AM500), while the enantiomeric excesses $\{\text{ee\%} = ([R] - [S]) \times 100/([R] + [S])\}$ were monitored by chiral gas chromatography [HP 5890 GC-FID, 30 m long Cyclodex-B (J&W Scientific) capillary column, carrier gas: He, 15 psi, 398 K, retention time for (*S*)-isomer: 31.8 min, for (*R*)-isomer: 32.5 min]. The ee values were reproducible within 2%. The product identification and the

enantiomeric excess in the case of PADA were monitored by gas chromatography [HP 5890 GC-FID, 30 m long Lipodex-A (Macherey–Nagel) capillary column, carrier gas: He, 15 psi, 318 K, retention time for (*S*)-isomer: 9 min, for (*R*)-isomer: 10 min].

3. Results and discussion

From catalysts that have proved suitable for the hydrogenation of EtPy, mainly Engelhard 4759 [23,24] and, occasionally, Johnson Matthey JMC94 were used for the experiments. AcOH, found to be the best in previous work was selected as solvent. In the course of the optimization of experimental conditions, work in the kinetic range was carried out mainly at room temperature and a hydrogen pressure of 1 bar, on the basis that other experience obtained during the hydrogenation of EtPy [24] and EBF [14] could also be made use of.

3.1. Studies on hydrogenation of ethyl-2-oxoglutarate

The (*R*)-EOTC is very frequently used synthon in the synthesis of natural products [27], but to the best of our knowledge, no satisfactory enantioselective heterogeneous catalytical method has been developed for its preparation.

According to Scheme 2 it was made the procedure for synthesis of (*R*)-EOTC. Some characteristic results of our studies on EOG hydrogenation are shown in Figs. 1–4. The most important conclusions are summarized below. Hydrogenation in the absence of chiral modifiers proceeds at a lower rate than does hydrogenation on catalysts modified with DHCD (Fig. 1), just like in the case of EtPy [6,24]. Increasing the concentration of the chiral modifier within the range studied results in a continuous increase in reaction rate. The minimal DHCD concentration necessary for achieving maximal enantioselectivity is 0.01–0.1 mmol l^{-1} at room temperature and a hydrogen pressure of 1 bar, in AcOH.

The courses of the curves representing conversion versus hydrogenation time are similar for the four parent cinchona alkaloids (Fig. 2). When CD and QN were used as modifiers, (*R*)-EOTC was formed, whereas with CN and QD with C8 and C9 carbon atoms of opposite configuration added as modifiers, (*S*)-EOTC was obtained; both products were of high optical purity. Under these mild experimental conditions the highest ee was observed on catalyst modified with QN.

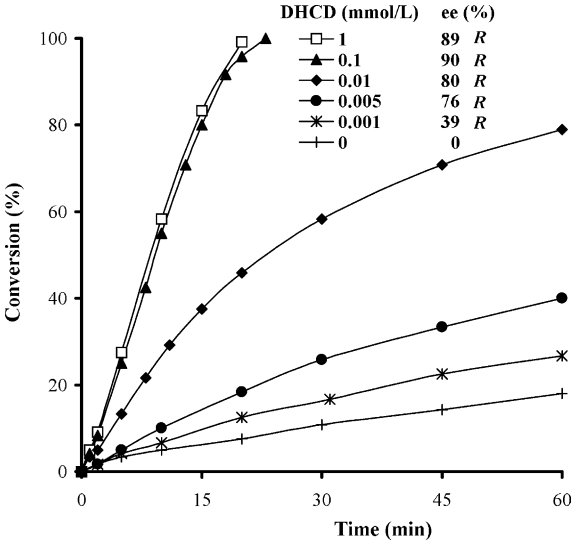


Fig. 1. Hydrogenation of EOG on DHCD-modified platinum (standard conditions).

It seems also clear that MeOHCD is the best modifier for the reaction, the ee values obtained mostly

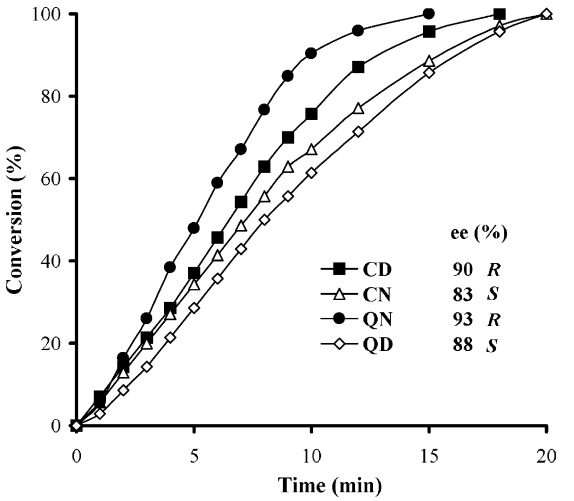


Fig. 2. Hydrogenation of EOG on parent cinchona alkaloid modified platinum (standard conditions, modifier concentration 1.5 mmol l^{-1}).

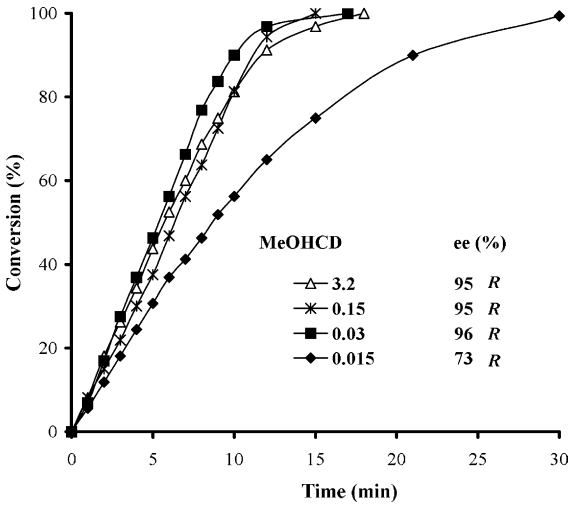


Fig. 3. Hydrogenation of EOG on MeOHCD-modified platinum (conditions: 50 mg JMC94, 5 ml AcOH, 1 bar H_2, 298 K, 1000 rpm, 0.25 ml EOG, MeOHCD concentration: 0.015–3.2 mmol/l).

exceed by ca. 5% those achieved with DHCD (Fig. 3). The JMC catalyst exhibited a slight but clear increase in both reaction rates and optical yields (5–6% ee increase) compared to E4759.

Since the enantioselective hydrogenation of α-ketoesters over the Pt-cinchona catalyst system generally shows better performance (higher reaction rates and optical yields) under elevated hydrogen pressures, the effect of hydrogen pressure, was also studied. The previous ee data indicate that the enantioselectivity of the reaction shows a slight hydrogen pressure dependence. Starting from 93% ee (1 bar H_2) the optical yields increased as a function of hydrogen pressure up to 96% ee. However, at 20 bar hydrogen pressure (Fig. 4) the ee seems to reach its maximum, and any further increase in hydrogen pressure does not result in higher optical yields.

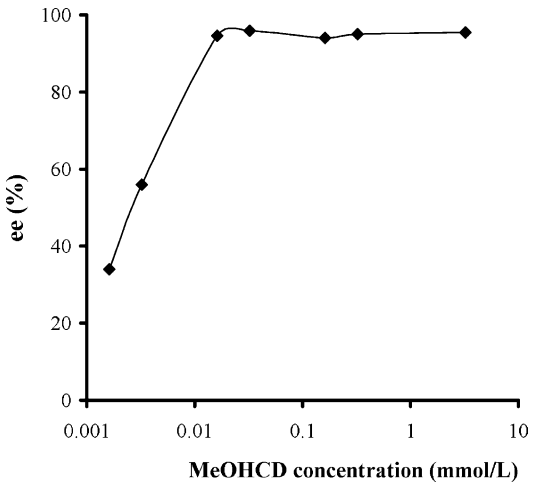


Fig. 4. Enantioselectivities–MeOHCD concentrations dependence in the hydrogenation of EOG (conditions: 50 mg E4759, 5 ml AcOH, 20 bar H_2, 297 K, 1200 rpm, 0.25 ml EOG, reaction time 60 min).

3.2. Studies on hydrogenation of pyruvaldehyde dimethyl acetal

The pyruvaldehyde dimethyl acetal is also a very frequently used synthon. Its importance in synthetic organic chemistry is the preparation of chiral O-protected α-hydroxy aldehydes [28]. PADA itself has already been reduced to the corresponding hydroxy derivatives by rhodium complexes, boranes or by enzymatic methods. Although each method is satisfactory, in cost or simplicity they cannot be compared to the cinchona modified Pt-catalyzed hydrogenations.

When optimizing the enantioselective hydrogenation of PADA, the effect of only one parameter, the concentration of the chiral modifier (DHCD) had to be varied, as—unexpectedly—an outstandingly high ee was observed already at the preliminary stage of the experiments [18], under the standard conditions selected for EtPy. Therefore further variations in hydrogen pressure and temperature as well as the use of other catalysts and solvents were judged unnecessary.

As shown by the experimental data in Fig. 5, at DHCD concentrations above 0.2 mmol l^{-1}, at room temperature and a hydrogen pressure of 1 bar, ee in excess of 96% can be achieved which is not decreased even at considerably higher DHCD concentrations, in contrast to EtPy, in the case of which a slight decrease was observed. Similarly to EtPy, however, reaction rate versus DHCD concentration also has a maximum in the case of PADA. Three explanations of these maxima for EtPy have been offered in [15,29,30]. It is quite remarkable that PADA is hydrogenated at a significantly slower rate than are EtPy and EOG. The DHCD concentration necessary for maximal ee is over 0.1 mmol l^{-1}.

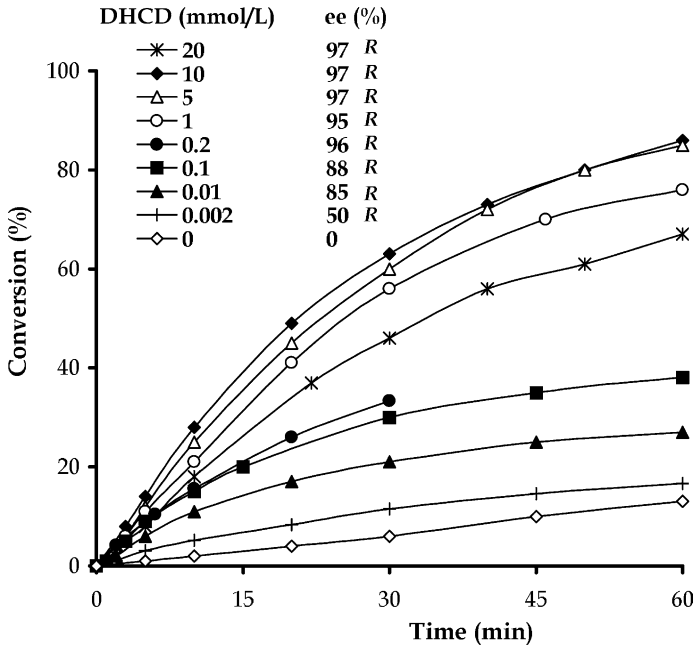


Fig. 5. Hydrogenation of PADA on DHCD-modified platinum (standard conditions).

3.3. *Interpretation of the enantioselective hydrogenation of activated ketones*

In the majority of studies aimed at the interpretation of enantioselective hydrogenation on platinum catalysts modified with cinchona alkaloids (Orito reaction) EtPy has been used as a model compound. These studies supported the mechanistic model proposed by Baiker, Blaser, Pfalz and Wells (see the latest reviews [9,10]) for the reaction in AcOH on Pt-alumina catalysts, a model based on hydrogen bonding interactions between an adsorbed modifier molecule and adsorbed EtPy. The basic starting point of this model was the concept of so-called ligand acceleration [31], based on the experimental observation that hydrogenation of EtPy in the presence of the chiral modifier is significantly faster than the unmodified reaction. The research groups involved in this research "agree that rate enhancement and enantiocontrol are closely connected effects and should be discussed together" [8–10]. We have recently called attention [24] to the possible role of a mechanism already proven to play a role in other reactions, i.e. electrostatic acceleration [32], associated with the presence of a newly recognized type of compound ($O^{+}[Al(OAc)_2]_3$ oxonium cations) [33].

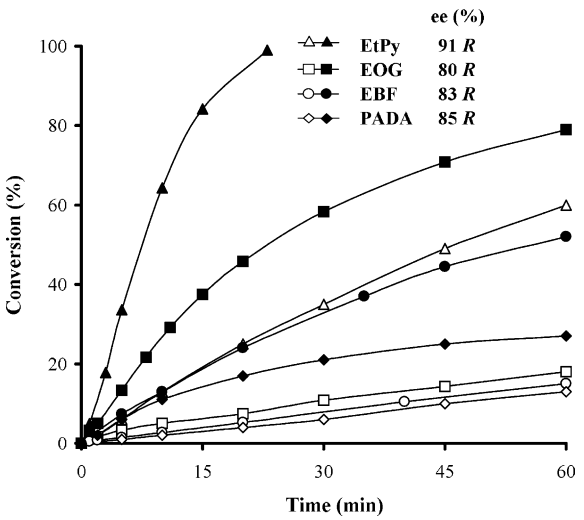


Fig. 6. Conversion–reaction time dependence in the enantioselective hydrogenations of activated ketones (standard conditions, DHCD concentration 0.01 mmol l^{-1}, 0.16 ml EBF: ethyl benzoylformate, open symbols: racemic hydrogenations, solid symbols: enantioselective hydrogenations).

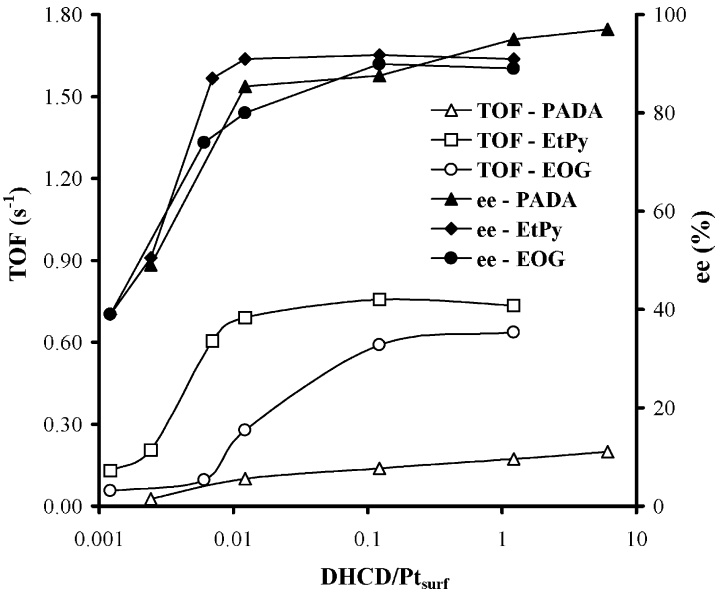


Fig. 7. Initial rate and enantioselectivity as functions of DHCD/$Pt_{surface}$ for hydrogenation of activated ketones (standard conditions).

The new experimental data presented in Figs. 6 and 7 on the examination of hydrogenations with high ee (EBF, EOG and PADA) under identical experimental conditions call attention to complementation of certain details about the reaction path of the enantioselective hydrogenation of activated ketones.

The main conclusions drawn from these experimental data are the following: (i) reaction rate increases in the order of PADA < EBF < EOG < EtPy; (ii) the ratio of the rate of the chiral reaction to that of the racemic reaction is substrate dependent; (iii) high ee may be achieved with substrates of various structures; (iv) the DHCD/$Pt_{surface}$ ratio necessary for the achievement of high ee is also substrate dependent. Experimental evidence indicating the importance of factors hitherto ignored has indeed been reported [14,15,34]; the data in Figs. 6 and 7 corroborate this evidence and justify the necessity of further investigation and interpretation.

4. Conclusion

The extremely high enantioselectivities (95–98%) achieved during hydrogenation of the compounds EBF, EOG and PADA indicate the investigating the following parameters and factors regarding the mechanism of the Orito reaction: adsorption of the individual substrates, nucleophilicity of the C=O group to be hydrogenated, interaction of substrates and cinchona alkaloids in solution, adsorption and stability of the resulting complex, cinchona alkaloid–substrate competition for adsorption on Pt, the role of product desorption in reaction kinetics (depending on the substrate), structure and stability of the Pt · modifier · substrate intermediate for various substrates, effect of the formation of chiral oxonium salts on reaction rate and ee.

The role of the above parameters has been extensively studied in the case of EtPy; however, similar studies have not been performed on the rest of the substrates. At the present state of affairs only questions and assumptions may be formulated which can only be answered and verified when experimental evidence becomes available. These studies naturally necessitate the application of various methods and their results may contribute to the elucidation of the origins of chiral induction and its further practical utilization.

Acknowledgements

Financial support by the Hungarian National Science Foundation (OTKA Grant T031707) and the

Hungarian Academy of Sciences (AKP 2000-20 2, 4) is highly appreciated.

References

[1] I. Ojima, Catalytic Asymmetric Synthesis, Wiley-VCH, Weinheim, 1993.
[2] R. Noyori, Asymmetric Catalysis, in: Organic Synthesis, Wiley, New York, 1994.
[3] G. Jannes, V. Dubois (Eds.), Chiral Reactions in Heterogeneous Catalysis, Plenum Press, New York, 1995.
[4] D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000.
[5] H.-U. Blaser, B. Pugin, M. Studer, in: D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000, pp. 1–17.
[6] A. Baiker, H.-U. Blaser, in: G. Ertl, H. Knözinger, J. Weitkamp (Eds.), Handbook of Heterogeneous Catalysis, vol. 5, Wiley-VCH, Weinheim, 1997, p. 2422.
[7] A. Pfaltz, T. Heinz, Top. Catal. 4 (1997) 229.
[8] H.-U. Blaser, H.-P. Jalett, M. Müller, M. Studer, Catal. Today 37 (1997) 441.
[9] P.B. Wells, R.P.K. Wells, in: D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000, pp. 123–154.
[10] A. Baiker, in: D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000, pp. 155–171.
[11] A. Tai, T. Sugimura, in: D.E. De Vos, I.F.J. Vankelecom, P.A. Jacobs (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000, pp. 173–209.
[12] Y. Orito, S. Imai, S. Niwa, J. Chem. Soc. Jpn. (1979) 1118; Y. Orito, S. Imai, S. Niwa, J. Chem. Soc. Jpn. (1980) 670.
[13] B. Török, K. Felföldi, G. Szakonyi, K. Balázsik, M. Bartók, Catal. Lett. 52 (1998) 81.
[14] M. Sutyinszki, K. Szöri, K. Felföldi, M. Bartók, Catal. Commun. 3 (2002) 125.
[15] C. LeBlond, J. Wang, J. Liu, A.T. Andrews, Y.-K. Sun, J. Am. Chem. Soc. 121 (1999) 4920;
C. LeBlond, J. Wang, J. Liu, A.T. Andrews, Y.-K. Sun, Top. Catal. 13 (2000) 169.
[16] M. Schürch, N. Künzle, T. Mallat, A. Baiker, J. Catal. 176 (1998) 569.
[17] N. Künzle, A. Szabo, M. Schürch, G. Wang, T. Mallat, A. Baiker, Chem. Commun. (1998) 1377.
[18] B. Török, K. Felföldi, K. Balázsik, M. Bartók, Chem. Commun. (1999) 1725.
[19] M. Studer, S. Burkhardt, H.-U. Blaser, Chem. Commun. (1999) 1727.
[20] M. von Arx, T. Mallat, A. Baiker, Tetrahedron: Asymmetry 12 (2001) 3089.
[21] K. Balázsik, K. Szöri, K. Felföldi, B. Török, M. Bartók, Chem. Commun. (2000) 555.
[22] K. Szöri, M. Sutyinszki, K. Felföldi, M. Bartók, Appl. Catal. A-Gen. 237 (2002) 275.
[23] M. Bartók, Gy. Szöllősi, K. Balázsik, T. Bartók, J. Mol. Catal. A-Chem. 177 (2002) 299.
[24] M. Bartók, K. Balázsik, Gy. Szöllősi, T. Bartók, J. Catal. 205 (2002) 168.
[25] S. Drioli, P. Nitti, G. Pitacco, L. Tossut, E. Valentin, Tetrahedron: Asymmetry 10 (1999) 2713.
[26] M. von Arx, T. Mallat, A. Baiker, J. Catal. 193 (2000) 161.
[27] G. Fronza, G. Fuganti, P. Grasselli, S. Servi, Chimia 47 (1993) 43.
[28] R.S. Atkinson, in: Stereoselective Synthesis, Wiley, Chichester, 1995.
[29] H.-U. Blaser, M. Garland, H.-P. Jalett, J. Catal. 144 (1993) 569.
[30] D. Ferri, T. Burgi, J. Am. Chem. Soc. 123 (2001) 12074.
[31] M. Garland, H.-U. Blaser, J. Am. Chem. Soc. 112 (1990) 7048.
[32] H. Jiao, P.V.R. Schleyer, J. Chem. Soc., Faraday Trans. 90 (1994) 1559.
[33] M. Bartók, P.T. Szabó, T. Bartók, Gy. Szöllősi, K. Balázsik, Rapid Commun. Mass Spectrom. 15 (2001) 65.
[34] H.-U. Blaser, D. Imhof, M. Studer, Stud. Surf. Sci. Catal. 108 (1997) 175.